UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,571	12/05/2003	Marie Anderson	100966-2 US	8775

44992 7590 08/23/2007

ASTRAZENECA R&D BOSTON
35 GATEHOUSE DRIVE
WALTHAM, MA 02451-1215

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
08/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,571	ANDERSON ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006 and 21 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11,48-51,54,55,57 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11,48-51,54,55,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 8-11, 48-51, 54-55, and 57-58 are pending in the application.

[2] Applicant's amendment to the claims, filed on 5/21/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed on 10/16/07, is acknowledged. Applicant is reminded of the amendment practice according to 37 CFR 1.121, which requires markings to show changes made relative to the prior version. The instant specification amendment to the "RELATED APPLICATIONS" (p. 2, top of the instant amendment) fails to show markings. See MPEP 714.

[4] Receipt of a sequence listing in computer readable form (CRF), a paper copy thereof, a statement of their sameness, and a statement that no new matter has been added to the specification by the paper copy of the sequence CRF, all filed on 5/21/07, is acknowledged.

Election/Restriction

[5] Applicant's election with traverse of Group I, claims 8-11, 48-51, 54-55, and 57-58, in the response filed on 5/21/07, is acknowledged. The traversal is on the ground(s) that Groups I, II, and III overlap in scope and thus would not require an undue burden on the examiner to co-examination all claims of Groups I, II, and III.

Applicant's argument is not found persuasive. Initially, it is noted that the claims that distinguished Groups I, II, and III, *i.e.*, claims 52-53 and 56, have been canceled,

with only the claims of Group I remaining. Thus, even assuming *arguendo* the examiner was persuaded by applicant's traversal, claims 52-53 and 56 are no longer pending and could not be rejoined.

Although the inventions of Groups I, II, and III are related as being crystals of *H. pylori* MurI, a separate search is required for each of Groups I, II, and III in view of the distinct space groups and/or unit cell dimensions of the crystals of each of Groups I, II, and III.

The requirement is still deemed proper and is therefore made FINAL.

[6] As only claims drawn to the elected invention remain pending, no claims have been withdrawn from consideration.

Sequence Compliance

[7] In order to perfect sequence compliance, applicant is required to submit an amendment directing entry of the sequence listing filed on 5/21/07 into the specification.

[8] The specification is objected to as failing to comply with the requirements for a sequence listing. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the

specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly the disclosed Figures 4 to 19 of the specification, listing structural coordinates representing the disclosure of an amino acid sequence. When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. See MPEP § 2422.02.

Claim Objection

[9] Claim 55 is objected to in the recitation of "P21." In order to maintain consistent formatting throughout the claims, it is suggested that "P21" in claim 55 be replaced with "$P2_1$".

Claim Rejections - 35 USC § 112, Second Paragraph

[10] Claim(s) 55 and 57-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 55 is confusing as being drawn to a crystal with a monoclinic space group of $P2_1$ with angles of $\alpha=\beta=\gamma=90^\circ$. However, according to "Crystallization of Nucleic acids and Proteins" (Ducruix and Giege, Ed., Oxford University Press, New York, 1999), a crystal with angles $\alpha=\beta=\gamma=90^\circ$ cannot have a space group of $P2_1$. See particularly p. 394, which shows that orthorhombic space group has angles $\alpha=\beta=\gamma=90^\circ$ and includes space groups P222, $P222_1$, $P2_12_12_1$, and $P2_12_12$ – monoclinic space group $P2_1$ is not included. It is suggested that applicant clarify the meaning of the claim.

[b] Claims 57-58 are indefinite in the recitation of "represented by." According to Encarta dictionary (encarta.msn.com), the term "represent" means to "be equivalent of something" or to "symbolize something." As such, it is unclear as to whether applicant intends for the claimed crystal to be limited to having the structural coordinates of Figure 5 or 6 or to be a crystal that is an equivalent to or is symbolized by the structural coordinates of Figure 5 or 6. If the latter, it is unclear as to how a skilled artisan would recognize the scope of crystals that are intended as being equivalent to or symbolized by the structural coordinates of Figure 5 or 6. It is suggested that applicant clarify the meaning of the term "represented by."

[c] Claims 57-58 are confusing as being drawn to a crystal that has structural coordinates as a skilled artisan would recognize that structural coordinates are

descriptive of a polypeptide complex, not a crystal of the polypeptide complex. It is suggested that applicant clarify the meaning of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

[11] The written description rejection of claim(s) 8-11 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. Claims 48-51, 54-55, and 57-58 are included in the instant rejection. Thus, claims 8-11, 48-51, 54-55, and 57-58 are rejected.

RESPONSE TO ARGUMENT: Beginning at the middle of p. 9 of the response filed on 10/16/06, applicant argues the amended claims are "directed only to the species of crystals of *H. pylori* MurI that were exemplified in the specification" and thus, the rejection is obviated by amendment.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification fails to adequately describe the genus of crystals as encompassed by the claims. According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

Claims 8-10 are drawn to a genus of crystals of SEQ ID NO:2 complexed with glutamate, the crystal having any space group and any unit cell dimensions. Claim 11 is drawn to a genus of crystals of SEQ ID NO:2 complexed with glutamate and an inhibitor having any structure, the crystal having any space group and any unit cell dimensions. Claims 48-51 are drawn to a genus of crystals of *H. pylori* MurI polypeptide complexed with glutamate, the polypeptide having any amino acid sequence that is considered to be an *H. pylori* MurI polypeptide. Claims 54-55 are drawn to a genus of crystals of *H. pylori* MurI polypeptide complexed with glutamate and an inhibitor, the polypeptide having any amino acid sequence that is considered to be an *H. pylori* MurI polypeptide and the inhibitor having any structure. Claim 57 is drawn to a genus of crystals of *H. pylori* MurI polypeptide complexed with glutamate, the crystal being "represented by" the coordinates of Figure 5, the polypeptide having any amino acid sequence that is considered to be an *H. pylori* MurI polypeptide and the crystal having any space group and unit cell dimensions. Claim 58 is drawn to a genus of crystals of *H. pylori* MurI polypeptide complexed with glutamate and an inhibitor, the crystal being "represented by" the coordinates of Figure 6, the polypeptide having any amino acid sequence that is considered to be an *H. pylori* MurI polypeptide, the inhibitor having any structure, and the crystal having any space group and unit cell dimensions.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical

and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 further states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In general, for a genus of crystals to be adequately described, the following must be adequately disclosed: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the specific protein and any molecule(s) bound to it, (2) the space group, and (3) the unit cell dimensions of the crystal.

While it is noted that the specification discloses representative species of crystals of an *H. pylori* MurI produced and purified according to the method set forth at pp. 90-95 of the specification having the space group and unit cell dimensions as set forth at p. 100, lines 20-22; p. 101, lines 9-11, 19-21, and 30-32, and p. 102, lines 8-10. Other than these representative species, the specification fails to disclose any other crystals of *H. pylori* MurI, which encompasses widely variant species as noted above. It is noted that while applicant may argue that *H. pylori* MurI polypeptide is well known and thus need not be specifically recited in claims 48-51, 54-55, and 57-58, as noted in a prior Office action, a number of variants of *H. pylori* MurI are known in the art. See, *e.g.*, Appendix A of the Office action mailed on 4/18/06, which shows an alignment of SEQ ID NO:2 with a known variant of *H. pylori* MurI.

Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[12] The scope of enablement rejection of claim(s) 8-11 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. Claims 48-51, 54-55, and 57-58 are included in the instant rejection. Thus, claims 8-11, 48-51, 54-55, and 57-58 are rejected.

RESPONSE TO ARGUMENT: Beginning at the bottom of p. 9 of the response filed on 10/16/06, applicant argues the amended claims are "encompass only the crystal species exemplified in the application" and thus, the rejection is obviated by amendment.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification fails to enable the full scope of crystals as encompassed by the claims. According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims...and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what

subject matter is encompassed by the claims...claims are to be given their broadest reasonable interpretation that is consistent with the specification."

Claims 8-10 broadly encompass a crystal of SEQ ID NO:2 complexed with glutamate, the crystal having any space group and any unit cell dimensions. Claim 11 broadly encompasses a crystal of SEQ ID NO:2 complexed with glutamate and an inhibitor having any structure, the crystal having any space group and any unit cell dimensions. Claims 48-51 broadly encompass a crystal of *H. pylori* MurI polypeptide complexed with glutamate, the polypeptide having any amino acid sequence that is considered to be an *H. pylori* MurI polypeptide. Claims 54-55 broadly encompass a crystal of *H. pylori* MurI polypeptide complexed with glutamate and an inhibitor, the polypeptide having any amino acid sequence that is considered to be an *H. pylori* MurI polypeptide and the inhibitor having any structure. Claim 57 broadly encompasses a crystal of *H. pylori* MurI polypeptide complexed with glutamate, the crystal being "represented by" the coordinates of Figure 5, the polypeptide having any amino acid sequence that is considered to be an *H. pylori* MurI polypeptide and the crystal having any space group and unit cell dimensions. Claim 58 broadly encompasses a crystal of *H. pylori* MurI polypeptide complexed with glutamate and an inhibitor, the crystal being "represented by" the coordinates of Figure 6, the polypeptide having any amino acid sequence that is considered to be an *H. pylori* MurI polypeptide, the inhibitor having any structure, and the crystal having any space group and unit cell dimensions. The broad scope of claimed crystals is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to enabling crystals of an *H. pylori* MurI

of SEQ ID NO:2 complexed with glutamate having the space group and unit cell dimensions as recited in claim 48, 49, 50, or 51.

The state of the art at the time of the invention acknowledges a high level of unpredictability for making a diffraction-quality protein crystal. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999; cited in the Office action mailed on 4/18/06) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995; cited in the Office action mailed on 4/18/06) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20; cited in the Office action mailed on 4/18/06), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). Also, the reference of Buts *et al.* (*Acta Crystallogr. D.* 61:1149-1159; cited in the Office action mailed on 4/18/06) teaches that "[f]ive naturally

occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups, with diffraction limits ranging between 2.4 and 1.1 Å resolution" and that crystallization of protein variants that differed from a parent sequence by only a single amino acid resulted in different crystal forms with distinct diffraction properties (see Tables 1-3). See also McPherson (*Eur. J. Biochem.*, 189 :1-23, 1990), which states (p. 13, 2nd column), "Table 2 lists physical, chemical and biological variables that may influence to a greater or less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids." Table 2 is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out, trying to pinpoint the variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can have huge influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the

probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual." Thus, in view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other *H. pylori* MurI polypeptides complexed with any inhibitor and optionally substrate, wherein the inhibitor is bound to any part of the *H. pylori* MurI polypeptide as encompassed by the claims can be achieved using the disclosed crystallization conditions.

Branden et al. acknowledges that solving the three-dimensional structure of a protein requires a diffraction-quality crystal (p. 374). In this case, while the specification discloses working examples of diffraction-quality *H. pylori* MurI crystals, the specification fails to provide the necessary guidance for crystallizing any other "*H. pylori* MurI" polypeptides complexed with *any* inhibitor and to generate any diffraction-quality crystal as encompassed by the claims. Further, it is noted that certain of the claims require "an inhibitor" and, while the specification discloses certain methods of making crystals of SEQ ID NO:2 with glutamate and the inhibitor of "compound A" (*e.g.*, specification at p. 103, top), neither the specification nor the prior art provide guidance for preparing "compound A."

While methods of protein crystallography were known at the time of the invention, it was not routine in the art to screen for all crystals of an "*H. pylori* MurI" polypeptide complexed with *any* inhibitor to generate a diffraction-quality crystal having any space group and any unit cell dimensions.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystals and polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

[13] Status of the claims:

- Claims 8-11, 48-51, 54-55, and 57-58 are pending.
- Claims 8-11, 48-51, 54-55, and 57-58 are rejected.
- No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656